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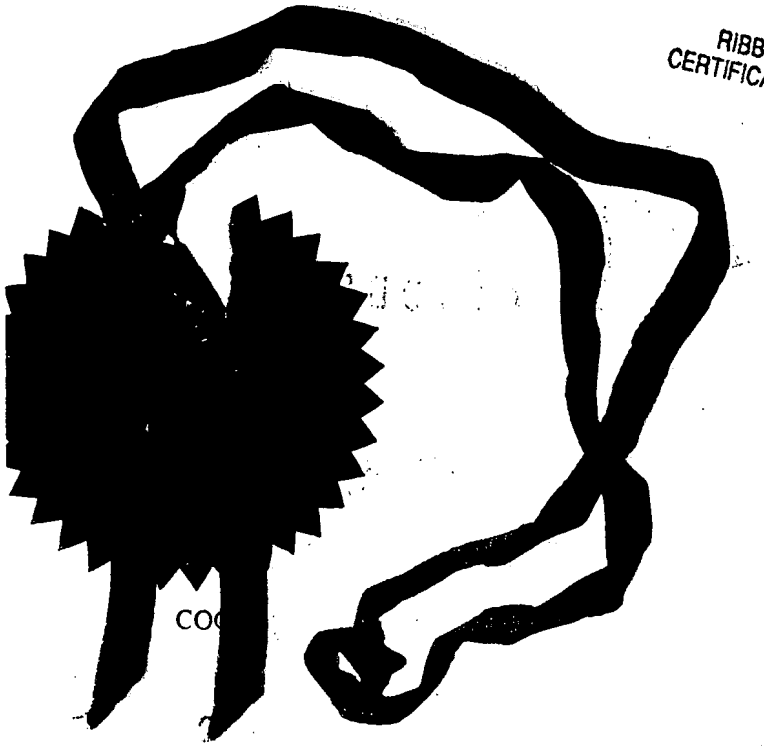

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PATENTS ACT 1977

25 OCT 1985

PATENTS FORM No. 1/77 (Revised 1982)

(Rules 16, 19)

25/10/85 B1212 PAT*** 10.00

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1985
26408

REQUEST FOR GRANT OF A PATENT

8526A08

THE GRANT OF A PATENT IS REQUESTED BY THE UNDERSIGNED ON THE BASIS OF THE PRESENT APPLICATION

I Applicant's or Agent's Reference *(Please insert if available)* JHFB/B1943

II Title of Invention CHEMICAL PROCESS

III Applicant or Applicants *(See note 2)*

Name (First or only applicant) Beecham Group p.l.c.

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Name (of second applicant, if more than one)

Country State

Address

IV Inventor (see note 3)

(a) The applicant(s) is/are the sole/joint inventor(s) or
(b) A statement on Patents Form No 7/77 is/will be furnished

V Name of Agent (if any) *(See note 4)* J.H.F. Blake | ADP CODE NO

VI Address for Service (See note 5)
Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey, KT18 5XQ, England

VII Declaration of Priority (See note 6)

Country	Filing date	File number

VIII The Application claims an earlier date under Section 8(3), 12(6), 15(4), or 37(4) (See note 7)

Earlier application or patent number and filing date

IX Check List *(To be filled in by applicant or agent)*

A The application contains the following number of sheet(s)		B The application as filed is accompanied by:-	
1 Request	1 Sheet(s)	1 Priority document	
2 Description	11 Sheet(s)	2 Translation of priority document	
3 Claim(s)	– Sheet(s)	3 Request for Search	
4 Drawing(s)	– Sheet(s)	4 Statement of Inventorship and Right to Grant	
5 Abstract	– Sheet(s)		

X It is suggested that Figure No – of the drawings (if any) should accompany the abstract when published.

XI Signature *(See note 8)* J.H.F. Blake — Chartered Patent Agent, Agent for the Applicants

NOTES:

1. This form, when completed, should be brought or sent to the Patent Office together with the prescribed fee and two copies of the description of the invention, and of any drawings.
2. Enter the name and address of each applicant. Names of individuals should be indicated in full and the surname or family name should be underlined. The names of all partners in a firm must be given in full. Bodies corporate should be designated by their corporate name and the country of incorporation and, where appropriate, the state of incorporation within that country should be entered where provided. Full corporate details, eg "a corporation organised and existing under the laws of the State of Delaware, United States of America," trading styles, eg "trading as xyz company", nationality, and former names, eg "formerly [known as] ABC Ltd." are not required and should not be given. Also enter applicant(s) ADP Code No. (if known).
3. Where the applicant or applicants is/are the sole inventor or the joint inventors, the declaration (a) to that effect at IV should be completed, and the alternative statement (b) deleted. If, however, this is not the case the declaration (a) should be struck out and a statement will then be required to be filed upon Patent Form No 7/77.
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6. The declaraton of priority at VII should state the date of the previous filing and the country in which it was made and indicate the file number, if available.
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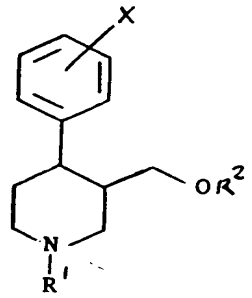
(6849) Dd 8818957 50M 5/84 SP&D Gp 606

CHEMICAL PROCESS

This invention relates to a novel chemical process for preparing aryl-piperidine carbinol ethers and to novel intermediates used in that process.

British patent no. 1422263 and US patent no 4007196 disclose compounds of formula A



A

in which R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl, R^2 represents an alkyl or alkynl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl, and X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio, or aralkyloxy.

The compounds of formula A are disclosed as having pharmacological properties that make them useful as anti-depressants.

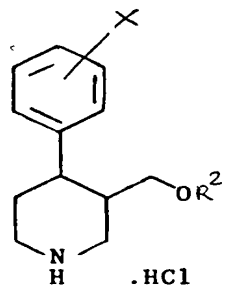
Among compounds of formula A in which R^1=H, a compound that has proved especially valuable is paroxetine (R^1=H, R^2=1,3-benzdioxylyl, X=F). More specifically, paroxetine is (-)-trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxy)methyl-piperidine.

In the above mentioned patents, compounds of formula A in which R^1=H may be obtained by hydrolysis of the corresponding compounds in which R^1 is an acyl group. The de-acylation may be part of a de-alkylation step to remove an N-alkyl protecting group introduced before addition of the group R^2 to the corresponding piperidine carbinol. More specifically, for the preparation of paroxetine (Examples 1 and 2 of US 4007196), an N-methyl compound (R^1=CH_3) is reacted with phenyl chloroformate and the resultant compound (R^1=$CO.OC_6H_5$) is hydrolysed with potassium hydroxide.

In a subsequent step, the compounds of formula A are converted into acid addition salts of the free base. US 4007196 discloses the formation of the maleic acid salt of paroxetine; GB 1422263 discloses the formation of hydrochlorides of other compounds in which R^1=H.

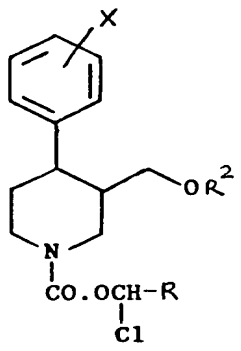
We have now discovered a new process for the preparation of compounds of formula A in which R^1=H by a de-acylation procedure which advantageously provides the desirable hydrochloride salt directly.

Accordingly, the present invention provides a process for the preparation of a compound of formula I



I

in which R^2 and X are as defined for formula A, by de-acylating a compound of formula II

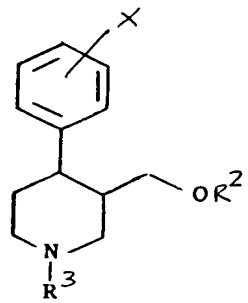


II

in which R is an alkyl group.

The de-acylation may be achieved by heating the compound of formula II in a lower alcohol e.g. methanol. Preferably R is a methyl group.

The de-acylation is advantageously carried out as the final step of a procedure for de-alkylating a compound of formula III

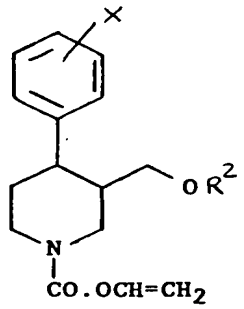


III

in which R^3 is an alkyl group.

The replacement of R^3 by R.CHClO.CO to convert the compound of formula III to the compound of formula II may be achieved by reacting the compound of formula III with α-chloro-ethyl chloroformate in a solvent such as dichloroethane or toluene.

Alternatively, the compound of formula III may be reacted with vinyl chloroformate in a solvent such as methylene dichloride or toluene to obtain the intermediate of formula IV



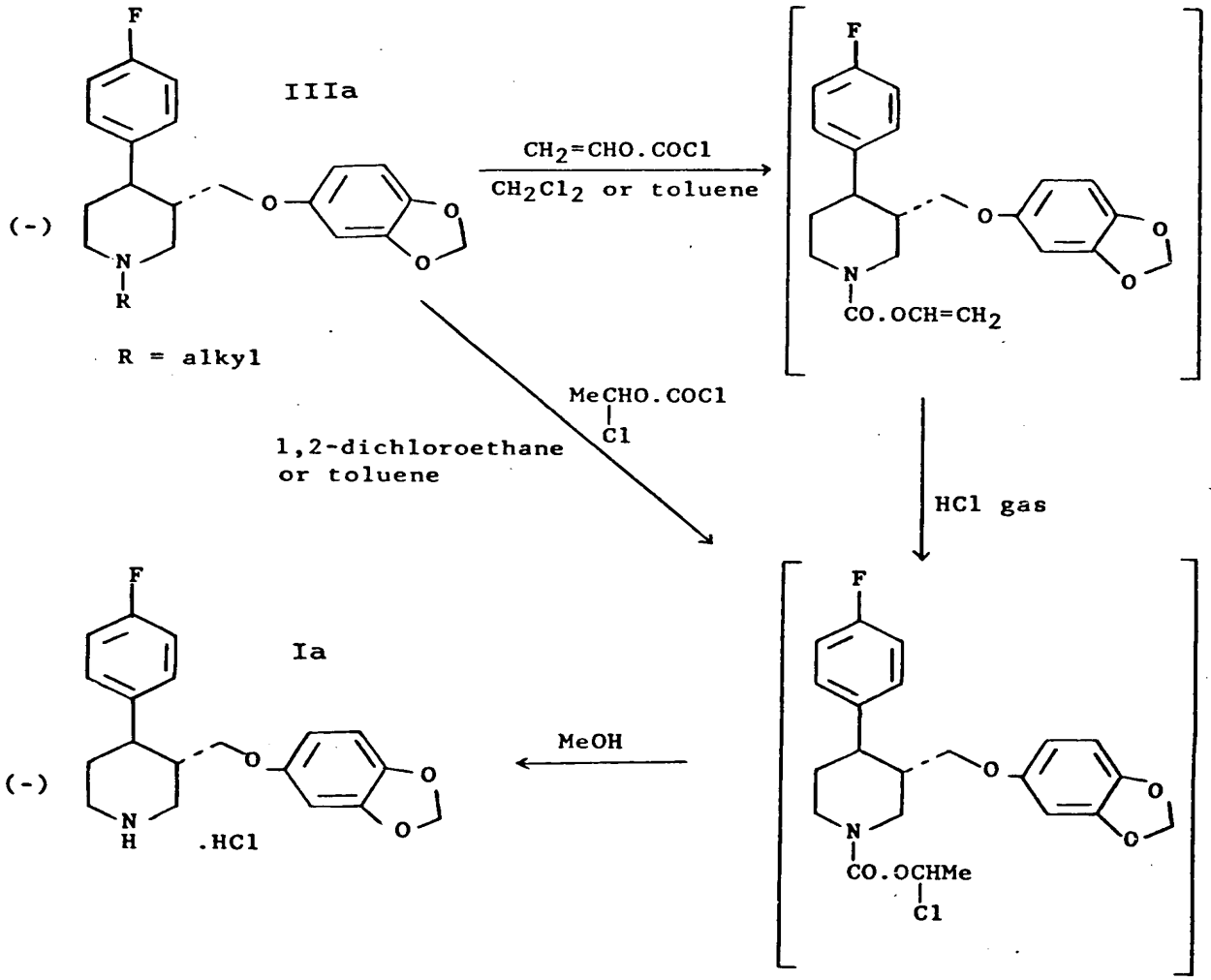
IV

which is then treated with HCl, preferably by passing HCl gas through the solution to obtain the compound of formula II.

An advantageous feature of the process of this invention is that the conversion of the compound of formula III into the compound of formula I can be carried out as a 'one-pot' process without isolating the intermediate of formula II or the intermediate of formula IV if the alternative route is followed.

The compounds of formula III may be prepared by the procedures set out in GB 1422263 and US 4007196.

Advantageously, the process of the present invention is used for the de-alkylation of a compound of formula IIIa to obtain paroxetine hyrochloride of formula Ia. This procedure is illustrated in the following reaction scheme.



The intermediates having the general formulae II and IV given above are novel compounds. They form part of the present invention, together with the processes for their preparation described herein.

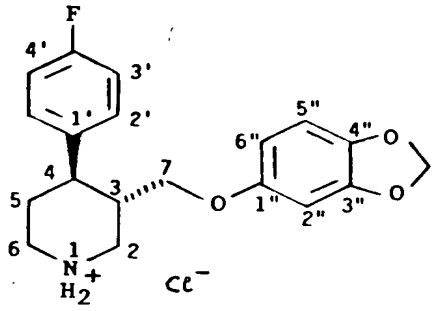
The present invention is illustrated by the following Examples; Examples 1 and 2 showing the route formula III-IV-II-I, Example 3 and 4 the route III-II-I. Temperatures are in °C.

Example 1

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylene-dioxyphenoxy)methylpiperidine hydrochloride

Vinyl chloroformate (6.42ml) was dissolved in 2ml dry methylene dichloride. The solution was cooled to 0° and the reaction flask purged with nitrogen. A solution of (-)-trans-4-(4'-fluorophenyl) -3-(3',4'-methylenedioxyphenoxy)methyl-N-methyl-piperidine (20g) in 52ml of dry methylene dichloride was added to the vinyl chloroformate solution over 30 minutes keeping the temperature below 0°. The mixture was allowed to warm to ambient temperature and stirred for 3 hours. The solution was then heated to reflux at 35° for a further 1 hour and cooled to -20°. Dry hydrogen chloride gas was bubbled into the solution for about 1 hour and the mixture allowed to stir at ambient temperature for 1 hour. Methanol (50ml) was added to the solution and the mixture heated under reflux for 1 hour, followed by addition of charcoal (4.5g) to the hot solution. Charcoal was filtered off after 10 minutes and the solvents removed in vacuo to give the crude product (21.4g). The solid was dissolved in isopropyl alcohol (140ml) and the solution filtered. The clear filtrate was cooled to 0° and seeded to allow the product to crystallise. After several hours at 0° the white solid was filtered off and the product slurried in water (30ml), filtered off, washed with water and dried to give the hydrochloride salt (15.8g, 74.1%).

^{1}H-n.m.r. (270 MHz, DMSO-d_6)



δ	Multiplicity	Assignment	
9.50	s, br, exch.	NH_2^+	2H
7.27	dd, $^4J_{HF}$=6Hz	2'	2H
7.17	dd, $^3J_{HF}$=9Hz	3'	2H
6.75	d	5''	1H
6.50	d	2''	1H
6.20	dd	6''	1H
5.94	s	O-CH_2-O	2H
3.61	dd }	7	2H
3.53	dd }		
3.50	m	2 eq	1H
3.39	d, br	6 eq	1H
3.03	ddd	6 ax	1H
2.97	dd	2 ax	1H
2.90	ddd	4	1H
2.58	m	3	1H
2.10	ddd	5 ax	1H
1.85	d, br	5 eq	1H

Example 2

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxy)methylpiperidine hydrochloride

The reaction described in Example 1 was repeated substituting 100ml of sodium dried toluene for 52 ml of dry methylene chloride. (-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxy)methyl-N-methyl-piperidine (20g) was converted to 16.5g of the hydrochloride salt in a yield of 77.4%.

The ^{1}H-n.m.r. spectrum was identical to that of the Example 1 product.

Example 3

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'methylenedioxy-phenoxy)methylpiperidine hydrochloride

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxy-phenoxy)methyl-N-methylpiperidine (10g) and N,N,N',N'-tetramethyl-1,8-naphthalenediamine (0.3g) were dissolved in 40ml of dry 1,2-dichlorethane (EDC) and the solution cooled to -3°. α-Chloroethyl chloroformate (3.22ml) in 5ml of dry EDC was added to the cold solution over 15 minutes. The mixture was stirred for 20 hours at ambient temperature and then heated to reflux for 2 hours. Methanol (15ml) was added to the solution and the mixture was refluxed for a further 2 hours. The mixture was washed with 20ml of 1N hydrochloric acid and the phases were allowed to separate. The organic layer was evaporated to dryness and the residue was dissolved in isopropyl alcohol (60ml). The hot solution was treated with charcoal (2g) and alumina (1.5g), stirred for 5 minutes and filtered hot. The clear solution was seeded and cooled to 0° for 18 hours. The white crystalline solid was filtered off and the wet product slurried in water (20ml). The solid was filtered off, washed with water and dried to give the hydrochloride salt (7.9g, 74.1%).

The ^{1}H-n.m.r. spectrum was the same as that of the Example 1 product.

Example 4

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylene-dioxyphenoxy)methyl-piperidine hydrochloride

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxy-phenoxy)methyl-N-methylpiperidine (10g) was dissolved in 45 ml of sodium dried toluene and the solution cooled to 5°. α-Chloroethyl chloroformate (3.22ml) in 5ml of dry toluene was added to the cold solution over 15 minutes. The mixture was stirred for 18 hours and methanol (15ml) was added to the mixture. The solution was stirred for 12 hours at ambient temperature. The solvent was then distilled off in vacuo and the residue dissolved in hot isopropyl alcohol (60ml). The hot solution was treated with charcoal (2g) and alumina (1.5g), stirred for 5 minutes, filtered and cooled to 0° for 18 hours. The white crystalline solid was filtered off, washed with a little isopropyl alcohol and the solid slurried in water (20ml). The solid was filtered off, washed with water and dried to give the hydrochloride salt (9.8g, 92%).

The ^{1}H-n.m.r. spectrum was identical to that of the Example 1 product.